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Fabry in the older patient: Clinical consequences and possibilities for treatment

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ABSTRACT

Baseline demographic and phenotypic characteristics of patients aged ≥50 years in the Fabry Outcome Survey (Shire; data extracted June 2014) were compared with younger adults to investigate potential factors influencing treatment decisions in later life. Age groups were defined using age at treatment initiation or at FOS entry for untreated patients: 18–49 (n = 1344; 49.5% male; 64.6% received agalsidase alfa enzyme replacement therapy [ERT]); 50–64 (n = 537; 35.4% male; 74.3% treated); 65–74 (n = 137; 32.1% male; 68.6% treated); and ≥75 years (n = 26; 26.9% male; 50.0% treated). Successive age groups showed higher median age at first symptom and diagnosis. Median alpha-galactosidase A activity, measured as percentage activity of the midpoint of the normal range, was much greater in females than males of all groups except ≥75 years (33.4% in females; 27.8% in males). Patients aged ≥75 years showed greater values than patients aged 18–49 years for median left ventricular mass indexed to height (62.7 vs 42.4 g/m$^{2.7}$), mean ventricular wall thickness (15.0 vs 10.0 mm) and prevalence of hypertension (57.7% vs 21.8%), and lower median estimated glomerular filtration rate (Modification of Diet in Renal Disease: 65.6 vs 98.5 mL/min/1.73 m^2). Larger proportions in the groups aged ≥50 exhibited cardiac and/or cerebrovascular manifestations compared with patients aged 18–49 years. The smaller proportion of patients receiving ERT aged ≥75 years compared with the younger groups might reflect relatively milder disease burden or physician/patient reluctance to initiate/continue ERT at this age. Further studies are needed to increase knowledge of Fabry disease and ERT in later life.

1. Introduction

Fabry disease results from a deficiency in lysosomal alpha-galactosidase A (α-Gal A) due to mutations in the *GLA* gene. This leads to the accumulation of globotriaosylceramide in cells and a multisystem pathology.

Despite Fabry disease being X-linked, female heterozygotes can experience all of the signs and symptoms of the disease, but generally later and with a milder, more variable phenotype than in males [1–4]. Females may, however, on occasions have a significant burden of disease, similar to that observed in males [5,6]. The overall life expectancy (calculated from birth) for patients with Fabry disease is 58 years for men and 75 years for women [7].

Two broad phenotypes of Fabry disease are now recognised, the classical form with childhood onset and multi-organ progression, and a later-onset phenotype with limited organ involvement presenting in middle age. In classical Fabry disease, α-Gal A activity is greatly diminished, at <1% of normal in males, whereas patients with later-onset cardiac or renal variants tend to have α-Gal A activity between 1% and 30% [8]. Diagnosis of the later-onset variant may be delayed due to lack of obvious external symptoms and signs such as acroparesthesia and angiokeratoma. In all Fabry disease phenotypes, the natural history of

Abbreviations: α-Gal A, alpha-galactosidase A; CKD EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; ERT, enzyme replacement therapy; FOS, Fabry Outcome Survey; LVH, left ventricular hypertrophy; LVMI, left ventricular mass indexed to height; MDRD, Modification of Diet in Renal Disease; MWT, mean ventricular wall thickness.

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aging may be difficult to distinguish from Fabry-specific complications, which themselves become more severe and prevalent with age.

Enzyme replacement therapy (ERT) in Fabry disease is expected to be most successful when started early in the disease course [9–11]; its initiation has been recommended as soon as early clinical signs of kidney, heart or brain involvement consistent with Fabry disease become apparent [12].

Family screening and symptom-based screening programmes have identified people with Fabry disease in later-life stages and it is unclear whether the rationale for starting treatment in this more advanced age group should be the same as for index cases diagnosed at a younger age. Symptom-based therapy in these older patients may be more beneficial, more cost effective and less burdensome to the health care provider than starting ERT to prevent Fabry disease progression and clinical events. Few studies focusing on elderly patients with Fabry disease have been performed; one analysis of six patients indicated limited benefit in starting/continuing ERT in elderly patients in terms of life expectancy and cost-effectiveness [13].

The objective of the present analysis was to describe the demographic and phenotypic characteristics of patients who were ≥50 years of age in the Fabry Outcome Survey (FOS) and to compare them with younger adult patients in an attempt to identify any factors that might influence the decision to treat, or not to treat, at later stages in life.

2. Methods

This was a retrospective analysis of data entered in FOS, a global, observational registry sponsored by Shire for the collection of outcomes data on Fabry disease. A diagnosis of Fabry disease is confirmed by reduced alpha-galactosidase A activity in plasma and leukocytes in males, and by molecular analysis to confirm *GLA* mutations in females and males. All patients with a confirmed diagnosis of Fabry disease who are receiving, or are eligible for ERT with agalsidase alfa, can be registered in FOS. Patients who are currently receiving ERT with a drug other than agalsidase alfa are not eligible for inclusion in FOS. Data collection in FOS was initiated in 2001, and all patients aged ≥18 years with data entered in FOS at the time of extraction (June 2014) were included.

The institution review boards of each participating centre approved FOS and all patients provided written informed consent prior to enrollment.

2.1. Populations analyzed

To analyze the presentation and clinical characteristics of elderly patients the population in FOS was divided into the following age groups: patients 18–49 years, 50–64 years, 65–74 years and ≥75 years (elderly group). The groups were stratified by age at treatment initiation for treated patients and age at FOS entry for untreated patients. Treated patients received agalsidase alfa 0.2 mg/kg body weight every other week.

2.2. Parameters evaluated

Patient demographics and the following baseline clinical characteristics were compared between the age groups: cardiac parameters (obtained via echocardiography, according to the American Society of Echocardiography recommendations) [14]: left ventricular mass indexed to height (LVMI), left ventricular hypertrophy (LVH; >48 g/$m^{2.7}$ in females and >50 g/$m^{2.7}$ in males), mean ventricular wall thickness (MWT), aortic root diameter; renal parameters: serum creatinine, estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) formula, Chronic Kidney Disease Epidemiology Collaboration (CKD EPI) equation, urine protein. Chronic kidney disease staging according to KDIGO guidelines [15] was performed for patients who had both eGFR and albumin data available (Supplementary data Fig. S1).

Baseline cardiac, renal, cerebrovascular and auditory signs/symptoms were also compared between the age groups of the overall population.

2.3. Statistical analysis

Descriptive statistics were calculated for all continuous and categorical variables to enable a thorough description of the demographic and clinical characteristics of patients aged ≥50 years.

3. Results

3.1. Enrollment and demographics

As of June 2014, a total of 2338 patients were enrolled in FOS (1279 females and 1059 males); 2044 of these were aged ≥18 years and are included in the current study. This study focuses on age rather than gender; however, data stratified by both age and gender are provided for reference in Supplementary data Tables S1–S4.

The proportion of females increased with successive age group (Table 1). The proportions of patients treated with ERT were 64.6% aged 18–49 years, 74.3% aged 50–64, 68.6% aged 65–74 and 50.0% aged ≥75 years (Table 1).

Median age at first symptom and diagnosis increased with each successive age group, whereas the median delay in diagnosis was similar between the groups aged 50–64 and 65–74 years (Table 1).

Median α-Gal A activity, measured as percentage activity of the midpoint of the normal range, was similar in females regardless of age, and generally much higher than in males. In the elderly group, α-Gal A activity was at its highest in males (27.8% [13.6–42.0%]) and thus closer to the level observed in females (33.4% [1.1–487.9%]; Table 1).

The largest proportion of Fabry disease diagnoses in each age group was made as a result of family members being affected. Of the specialists who first suspected Fabry disease, cardiologists diagnosed the largest proportions of patients in all groups aged ≥50 years. Nephrologists diagnosed the largest proportion of patients aged 18–49 years (Table 1).

The majority of patients were negative for heart pacemaker/transplant/defibrillator use at any time (Table 1). Therapy with angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers was more prevalent in patients who were aged ≥50 years than in younger adults (Table 1). Diabetes mellitus was more prevalent in patients aged ≥50 years than in younger adults (6.1% aged 50–64; 10.9% aged 65–74 and 3.8% aged ≥75 years vs 1.4% aged 18–49 years), and hypertension prevalence decreased with decreasing age group (57.7% aged ≥75 years; 48.2% aged 65–74; 41.9% aged 50–64; 21.8% aged 18–49; Table 1).

3.2. Phenotypic characteristics

3.2.1. Baseline cardiac parameters and events

A higher median baseline LVMI was demonstrated by Fabry patients presenting at a more advanced age than in the youngest group (Fig. 1A). Similarly, median MWT was progressively higher in the older groups (Fig. 1B).

Median aortic root diameter was similar for each of the age groups (see Supplementary data Table S2 for aortic root diameter by gender).

The rate of cardiac events/manifestations experienced before treatment initiation or FOS entry was greater in patients aged >50 years, where similar rates were experienced by the groups aged 50–64 (81.0%) and 65–74 (80.3%), and the highest rate (88.5%) by the elderly group. Fewer patients experienced any cardiac event/manifestation in the youngest group (58.6%; Table 2). Left ventricular hypertrophy was the most prevalent cardiac manifestation in each age group (Table 2).

Table 1
Summary of demographics and general clinical characteristics of the overall FOS population, stratified by age group (and gender for α-Gal A activity).

Parameter	18–49 years		50–64 years		65–74 years		≥75 years	
Overall	*N* = 1344		*N* = 537		*N* = 137		*N* = 26	
Males, n (%)	679 (50.5)		347 (64.6)		93 (67.9)		19 (73.1)	
Females, n (%)	665 (49.5)		190 (35.4)		44 (32.1)		7 (26.9)	
Treated, n (%)	868 (64.6)		399 (74.3)		94 (68.6)		13 (50.0)	
Males, n (%)	572 (65.9)		161 (40.4)		30 (31.9)		3 (23.1)	
Females, n (%)	296 (34.1)		238 (59.6)		64 (68.1)		10 (76.9)	
Age (years) at first symptom								
N (missing)	857 (487)		315 (222)		77 (60)		15 (11)	
Mean (SD)	16.6 (11.9)		32.2 (18.8)		47.8 (19.2)		53.8 (23.8)	
Median (range)	12.0 (0.0–49.0)		34.0 (0.0–63.0)		54.0 (4.0–71.0)		64.0 (4.0–75.0)	
Age (years) at diagnosis								
N (missing)	1276 (68)		505 (32)		128 (9)		25 (1)	
Mean (SD)	28.3 (11.5)		50.1 (11.2)		63.4 (10.3)		70.3 (13.1)	
Median (range)	29.0 (0.0–50.0)		52.0 (4.0–64.0)		66.0 (11.0–74.0)		75.0 (36.0–85.0)	
Delay (years) between symptom and diagnosis								
N (missing)	847 (497)		311 (226)		75 (62)		15 (11)	
Mean (SD)	10.9 (12.0)		16.3 (17.2)		14.7 (18.0)		12.8 (25.7)	
Median (range)	8.0 (−33.0–41.0)		11.0 (−25.0–55.0)		10.0 (−35.0–62.0)		6.0 (−27.0–68.0)	
Age (years) at start of agalsidase alfa								
N (missing)	868 (476)		399 (138)		94 (43)		13 (13)	
Mean (SD)	35.2 (9.2)		56.6 (4.1)		69.1 (2.8)		77.7 (1.9)	
Median (range)	35.6 (18.0–49.9)		56.3 (50.0–64.9)		68.6 (65.0–75.0)		78.7 (75.0–80.8)	
Time (years) to follow up								
N (missing)	1344 (0)		537 (0)		137 (0)		26 (0)	
Mean (SD)	3.8 (3.4)		2.9 (3.0)		2.5 (2.5)		1.8 (2.4)	
Median (range)	2.9 (0.0–12.4)		1.9 (0.0–12.1)		1.7 (0.0–10.1)		0.9 (0.0–10.5)	
Relatives in the cohort, n (%)	645 (48.0)		222 (41.3)		56 (40.9)		16 (61.5)	
α-Gal A (% midpoint normal range)	Male	Female	Male	Female	Male	Female	Male	Female
N (missing)	288 (377)	323 (356)	87 (103)	158 (189)	21 (23)	33 (60)	2 (5)	11 (8)
Mean (SD)	6.3 (7.6)	51.5 (36.6)	8.1 (9.6)	52.4 (35.1)	10.3 (13.8)	60.4 (60.7)	27.8 (20.1)	89.7 (142.0)
Median (range)	4.0 (0.0–66.7)	44.0 (0.1–212.0)	5.2 (0.0–50.0)	47.6 (0.1–181.8)	7.7 (0.2–67.0)	44.0 (0.2–251.5)	27.8 (13.6–42.0)	33.4 (1.1–487.9)
Specialist who first suspected disease, n (%)	414		182		45		6	
Affected family member	470 (50.5)		139 (39.2)		38 (41.3)		11 (55.0)	
Cardiologist	41 (4.4)		52 (14.6)		24 (26.1)		4 (20.0)	
Dermatologist	39 (4.2)		14 (3.9)		–		–	
Gastroenterologist	1 (0.1)		1 (0.3)		–		–	
General practitioner	32 (3.4)		9 (2.5)		2 (2.2)		–	
Geneticist	37 (4.0)		42 (11.8)		6 (6.5)		4 (20.0)	
Internist	21 (2.3)		8 (2.3)		3 (3.3)		–	
Nephrologist	120 (12.9)		30 (8.5)		7 (7.6)		1 (5.0)	
Neurologist	37 (4.0)		18 (5.1)		1 (1.1)		–	
Ophthalmologist	52 (5.6)		17 (4.8)		3 (3.3)		–	
Other	36 (3.9)		19 (5.4)		6 (6.5)		–	
Paediatrician	38 (4.1)		4 (1.1)		2 (2.2)		–	
Rheumatologist	6 (0.6)		2 (0.6)		–		–	
ARB/ACE therapy any time, n (%)	408 (30.4)		238 (44.3)		72 (52.6)		10 (38.5)	
Heart pacemaker/transplant/defibrillator, n (%)	10 (0.7)		21 (3.9)		4 (2.9)		2 (7.7)	
Currently smoking, n (%)	103 (7.7)		28 (5.2)		2 (1.5)		–	
Smoking history, n (%)	171 (12.7)		78 (14.5)		18 (13.1)		5 (19.2)	
Diabetes mellitus, n (%)	19 (1.4)		33 (6.1)		15 (10.9)		1 (3.8)	
Hypertension, n (%)	293 (21.8)		225 (41.9)		66 (48.2)		15 (57.7)	
Obesity (≥35 kg/m^2), n (%)	38 (2.8)		23 (4.3)		4 (2.9)		1 (3.8)	
Tortuous vessels, n (%)	213 (15.8)		60 (11.2)		15 (10.9)		1 (3.8)	
Angiokeratoma, n (%)	642 (47.8)		194 (36.1)		48 (35.0)		5 (19.2)	
Raynaud Syndrome, n (%)	124 (9.2)		46 (8.6)		13 (9.5)		1 (3.8)	
Malignancy, n (%)	17 (1.3)		24 (4.5)		9 (6.6)		5 (19.2)	
Deceased recorded in database, n (%)	41 (3.1)		39 (7.3)		13 (9.5)		4 (15.4)	

ACE = angiotensin-converting enzyme inhibitor; α-Gal A = alpha-galactosidase A; ARB = angiotensin receptor blocker.

3.2.2. Baseline renal parameters and events

Median serum creatinine was similar in all age groups: 0.8 (range 0.4–14.6), 0.9 (0.3–13.7), 1.0 (0.5–11.7) and 0.9 (0.6–10.3) mg/dL in patients aged 18–49, 50–64, 65–74 and ≥75 years, respectively.

As expected, median eGFR calculated using the MDRD equation showed a decrease with increasing age group and was lowest in the elderly group (Fig. 1C).

Similarly, median (range) eGFR calculated using the CKD-EPI formula also showed a decrease with increasing age group, from 107.0 (0.0–172.6) mL/min/1.73 m^2 in patients aged 18–49 to 82.1 (3.0–117.7), 68.1 (3.9–101.4) and 60.8 (4.4–89.6) mL/min/1.73 m^2 in patients aged 50–64, 65–74 and ≥75 years, respectively.

Median urine protein levels were 168.2 (range 0.0–4900.0), 148.2 (20.0–4640.0) and 110.0 (47.6–2010.0) mg/24 h in the groups aged 50–64, 65–74 and ≥75 years, respectively, compared with 167.0 (0.0–9690.0) mg/24 h in the youngest group.

Any renal event/manifestation was experienced by a similar percentage of patients in each of the age groups: 46.0% in patients aged 18–49 years, and 49.9%, 46.0% and 46.2% in patients aged 50–64, 65–74 and ≥75 years, respectively. Proteinuria/microalbuminuria was the most prevalent renal manifestation in all age groups (Table 2).

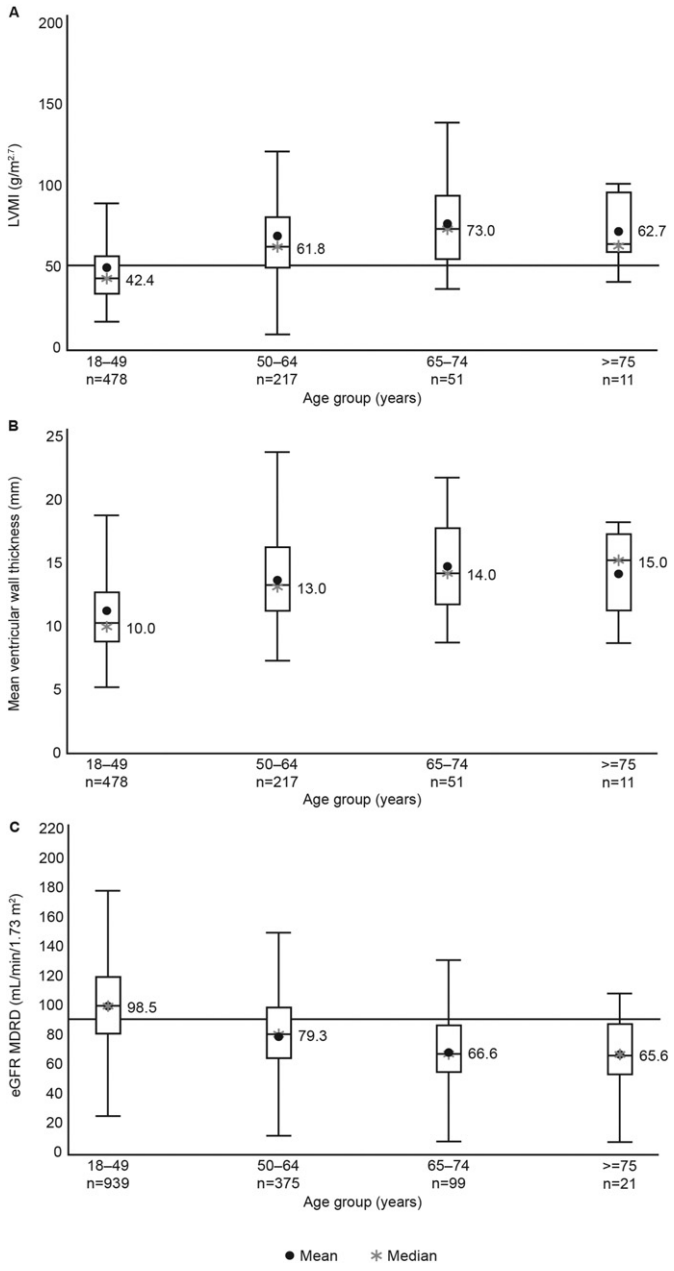

Fig. 1. Box plots showing A. Left ventricular mass indexed to height. B. Mean ventricular wall thickness. C. Estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease formula (MDRD) for the patients in each age group.

Chronic kidney disease staging according to KDIGO guidelines [15] is summarized in Supplementary data Fig. S1.

3.2.3. Isolated cardiac and renal manifestations

The proportion of patients who reported isolated cardiac manifestations (defined as LVH but no proteinuria) was highest in the elderly group (61.5%; $n = 16$) and decreased with decreasing age: 39.4% ($n = 54$), 38.5% ($n = 207$) and 16.9% ($n = 227$) in the groups aged 65–74, 50–64 and 19–50 years, respectively.

Conversely, the proportion of patients with isolated renal manifestations (defined as proteinuria but no LVH) was lowest in the elderly group (3.8%; $n = 1$) and increased with decreasing age: 4.4% ($n = 6$), 7.1% ($n = 38$) and 18.8% ($n = 253$) in the groups aged 65–74, 50–64 and 18–49 years.

3.2.4. Cerebrovascular events

Any cerebrovascular event/manifestation was reported by a greater proportion of patients in the groups aged 50–64 (24.2%), 65–74 (27.7%) and ≥75 years (19.2%) than in the youngest group (17.1%). Stroke was most prevalent in the groups older than 50 years (Table 2).

3.2.5. Auditory events

A larger proportion of patients in the elderly group (57.7%) experienced auditory events/manifestations than in the youngest group (45.7%). Hearing impairment was most prevalent in the elderly group (Table 2).

4. Discussion

This study analyzed data collected in FOS to investigate whether a demographic and phenotypic description could be made of patients aged ≥50 years that differentiate them from younger adult patients.

This analysis showed that a smaller proportion of older patients were treated with ERT and that, after 50 years of age, the majority of ERT initiations were made in female patients (Table 1). This indicates a possible reluctance of physicians and patients to commence and/or continue ERT at older ages. The decision to either initiate or continue long-term ERT in patients with Fabry disease who are aged ≥50 years must take into account potential treatment benefits over costs to the healthcare system, and quality of life. Factors for consideration regarding ERT initiation in elderly patients are outlined in Fig. 2 [16].

Since Fabry disease is a progressive disorder, disease severity and the degree of organ involvement increase with age. Several recent reports have indicated that ERT in patients with advanced disease has limited effectiveness [17–19], especially when initiated after fibrosis has started to develop in the heart, kidney or central nervous system, which may occur at a relatively early age in Fabry disease [20]. One study on patients who were slightly older (40 ± 9 years) than in previously studied groups, and who were thus likely to have more advanced disease, found that disease progression towards organ failure and death was not halted by ERT over a period of approximately 6 years [18]. Initiating/continuing ERT in patients with Fabry disease who are ≥75 years may not be beneficial in terms of life expectancy or cost effectiveness [13]. The number of years since symptom onset or diagnosis may be a better predictor of ERT refractory disease than simply age.

The cardiac and renal signs and symptoms observed in the analysis population aged ≥50 years were generally non-specific and could reflect the natural aging process. For example, compared with patients aged 18–49 years, older patients had a greater prevalence of cardiac events/manifestations such as LVH and arrhythmia, decreases in eGFR and increased prevalence of hearing impairment. Hearing loss, a common occurrence during natural aging, was previously found to be independently predictive of cardiac, renal and cerebrovascular complications in Fabry disease [21] and was the most prevalent auditory event in the current study. Microalbuminuria is a known cardiovascular risk factor in patients with hypertension [22], and microalbuminuria and proteinuria were the most prevalent renal manifestations in each age group in the current analysis. While the prevalence of hypertension increased with successive age group, the prevalence of microalbuminuria and proteinuria did not. Since the groups were stratified by age at treatment initiation or FOS entry in untreated patients, this finding may reflect a lower burden from microalbuminuria/proteinuria and a milder Fabry disease phenotype in the older age groups than the younger group.

Whether patients have classical or later-onset Fabry disease may also require consideration when making decisions regarding ERT initiation/continuation. We found that age at symptom onset generally increased with successive age group. These data were collected via patient recall, and thus must be interpreted carefully, but this increase may reflect a predominance of de novo diagnosis of the later-onset phenotype in the groups aged ≥50 years, rather than long-lived patients

Table 2
Summary of cardiac, renal, cerebrovascular and auditory events/manifestations among the overall FOS population, stratified by age group.

Parameter	18–49 years ($n = 1344$)	50–64 years ($n = 537$)	65–74 years ($n = 137$)	≥75 years ($n = 26$)
Any cardiac event/manifestation, n (%)	787 (58.6)	435 (81.0)	110 (80.3)	23 (88.5)
Conduction abnormality	94 (7.0)	80 (14.9)	26 (19.0)	6 (23.1)
Fatigue	317 (23.6)	129 (24.0)	40 (29.2)	10 (38.5)
LVH	431 (32.1)	336 (62.6)	93 (67.9)	20 (76.9)
Heart failure	205 (15.3)	122 (22.7)	42 (30.7)	9 (34.6)
Arrhythmia	120 (8.9)	111 (20.7)	49 (35.8)	13 (50.0)
Cardiac surgery	15 (1.1)	29 (5.4)	10 (7.3)	4 (15.4)
Palpitations	220 (16.4)	111 (20.7)	27 (19.7)	6 (23.1)
Angina	44 (3.3)	54 (10.1)	18 (13.1)	1 (3.8)
Valve disease	125 (9.3)	75 (14.0)	24 (17.5)	7 (26.9)
Cardiac syncope	28 (2.1)	17 (3.2)	3 (2.2)	4 (15.4)
Dyspnea	131 (9.7)	108 (20.1)	39 (28.5)	7 (26.9)
Other (than listed)	129 (9.6)	115 (21.4)	33 (24.1)	6 (23.1)
Any renalevent/manifestation, n (%)	618 (46.0)	268 (49.9)	63 (46.0)	12 (46.2)
Microalbuminuria	222 (16.5)	74 (13.8)	23 (16.8)	5 (19.2)
Peritoneal dialysis	8 (0.6)	2 (0.4)	–	–
Proteinuria	457 (34.0)	167 (31.1)	45 (32.8)	5 (19.2)
Hematuria	82 (6.1)	29 (5.4)	7 (5.1)	1 (3.8)
Other (than listed)	79 (5.9)	56 (10.4)	18 (13.1)	4 (15.4)
Renal failure	116 (8.6)	71 (13.2)	18 (13.1)	2 (7.7)
Hemodialysis	42 (3.1)	19 (3.5)	2 (1.5)	–
Transplants	30 (2.2)	20 (3.7)	2 (1.5)	–
Unspecified dialysis	36 (2.7)	21 (3.9)	2 (1.5)	2 (7.7)
Any cerebrovascular event/manifestation, n (%)	230 (17.1)	130 (24.2)	38 (27.7)	5 (19.2)
TIA	49 (3.6)	32 (6.0)	7 (5.1)	1 (3.8)
Other (than listed)	122 (9.1)	44 (8.2)	14 (10.2)	2 (7.7)
Stroke	96 (7.1)	73 (13.6)	26 (19.0)	4 (15.4)
PRIND	4 (0.3)	5 (0.9)	–	–
Any auditory event/manifestation, n (%)	614 (45.7)	256 (47.7)	64 (46.7)	15 (57.7)
Tinnitus	400 (29.8)	123 (22.9)	27 (19.7)	6 (23.1)
Vertigo	318 (23.7)	132 (24.6)	31 (22.6)	4 (15.4)
Sudden deafness	43 (3.2)	19 (3.5)	4 (2.9)	1 (3.8)
Hearing impairment	297 (22.1)	156 (29.1)	45 (32.8)	13 (50.0)
Other (than listed)	31 (2.3)	20 (3.7)	7 (5.1)	3 (11.5)

LVH = left ventricular hypertrophy; PRIND = prolonged reversible neurological deficits; TIA = transient ischemic attack.

with early onset classical phenotypes. Furthermore, age at diagnosis tended to increase with successive age group and each group also experienced delays in diagnosis, as found previously [3,4]. The delay in diagnosis doubled between the ages of 50 and 74 years, possibly because patients presenting in these groups had limited disease with fewer symptoms characteristic of Fabry disease. Angiokeratoma and tortuous ocular vessels, which may facilitate Fabry disease diagnosis, were more prevalent in patients aged 18–49 years than in the older age groups. Since the level of tortuosity is positively correlated with disease severity [23], this could provide further evidence of limited disease in our population aged ≥50 years.

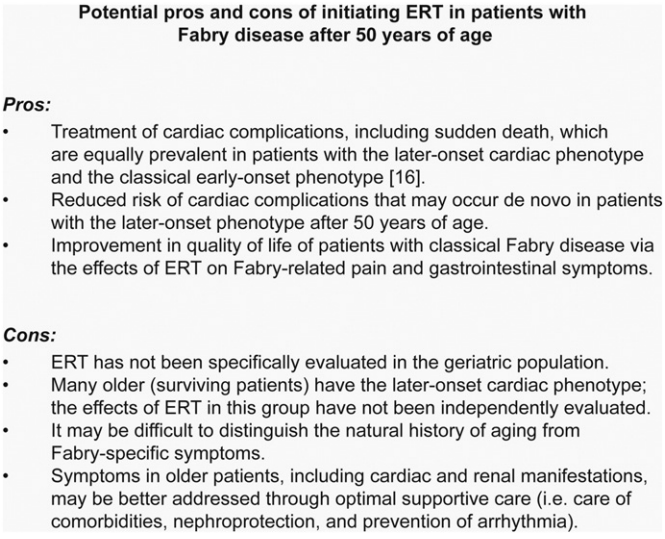

Fig. 2. Considerations in the decision to initiate ERT in patients with Fabry disease who are older than 50 years.

Age at onset in patients with cardiac variant Fabry disease is reported to be in the sixth to eighth decade [8]. In our study, compared with the younger adult group, the prevalence of cardiac events/manifestations was greater in patients aged 65–74 and ≥75 years, whereas that of renal events/manifestations generally remained similar or was lower. The cardiac events in this group may be linked to the aging process or they might indicate a larger proportion of patients aged 65 years and above with the later-onset cardiac variant of Fabry disease. If the main value of ERT is considered to be preventing significant clinical events that might only occur years hence resulting from a lifetime of storage deposition and secondary organ pathology, then the value of ERT in these patients may be limited. However, it remains possible that, for those experiencing Fabry symptoms not alleviated by conventional therapies, ERT might have a role in immediate symptomatic benefit. An improvement in symptoms has been reported when ERT is started in younger patients [24], but the efficacy of ERT in later-onset Fabry disease still needs to be formally determined and a regimen for optimal supportive care and symptom control carefully considered. Similarly, in classical patients receiving long-term ERT, there is likely to come a point at which supportive and symptomatic care becomes more important than limited ERT for long-term organ protection.

There were a number of limitations in our study. FOS is a rare disease registry, and thus contains a relatively small number of patients, especially in the older age groups. However, few exclusion criteria were

applied; therefore the patient population was not highly selected. Furthermore, a decline in number with aging would be expected in a control population, although the low numbers did limit us to the use of descriptive statistics only, making it difficult to draw conclusions from the data. The possibility of errors incurred during data entry cannot be completely ruled out. While some values appeared to be high (for example, upper range value for urine protein of 9690.0 mg/24 h in the youngest group), these were considered to be within clinically feasible ranges; those that were deemed implausible were excluded from analysis. Also, due to some missing data, the trends observed will need to be followed up in order to be confirmed. Definitions of signs and symptoms are not provided in FOS and thus are not standardized across participating centres. Each physician determines their presence at patient visits according to predetermined criteria and records this information in the database primarily as "YES" or "NO" variables. Further information on particular signs and symptoms is sparse, which imposes some restrictions on the analyses that can subsequently be performed. It should also be noted that standardized methods for measuring the clinical parameters are not currently specified within FOS. A further possible limitation is that genetics data were not available for inclusion; however, this paper represents a phenotypic analysis and reports data, including residual α-Gal A activity data, from a large number of patients. Mutations associated with later-onset variants of Fabry disease could prove to be an interesting focus for future studies.

5. Conclusions

This is the first report to date analyzing the phenotype of Fabry disease in patients aged ≥50 years. Some elderly patients who are experiencing Fabry-related complications and who are eligible for ERT are not receiving it. Further studies are required to delve deeper into the reasons behind this, to show what types of supportive care are being provided instead of or as well as ERT, and also to better define those who are suitable for ERT. Although there may be limited benefits in initiating or continuing ERT in older patients with more advanced Fabry disease, further investigations are warranted, particularly in older patients with later-onset disease who may show a slower progression of Fabry manifestations.

Disclosure statement

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Informed consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for inclusion in the study.

Author contributions

Olivier Lidove, Frédéric Barbey and Derralynn Hughes developed the initial draft of the manuscript. Svetlana Bizjajeva performed the statistical analyses. All authors were involved in the acquisition, analysis, and/or interpretation of the data and participated in revising the manuscript critically for important intellectual content and approved the final version to be published.

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Appendix A. Supplementary data

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